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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/670,119	06/25/96	NG G	SIM-001(7434

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	20

DATE MAILED: 12/14/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic(s)
08/670,119	Ng et al
Examiner	**Group Art Unit**
Robert C. Hayes	1645

☒ Responsive to communication(s) filed on *Sep 28, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *18, 20-37, and 60-65* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *18, 20-37, and 60-65* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. The amendment filed 09/28/99 has been entered.

2. Applicant's arguments filed 09/28/99 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 18, 20-37 & 60-65 are again rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons made of record, and as follows.

Applicants argue that: a) "claims 25-27... , 30-31..., and 33-34, as well as the claims which are dependent on these claims, do in fact recite a 'specific receptor' to be inhibited and do, in fact, recite 'structurally defined components' in the form of amino acid sequences", and that "[f]urthermore, claims 28, 32, and 35 further limit these claims by reciting the specific disorders which are treated", and therefore, "fully enabled" "with respect to these claims". In contrast to Applicants' assertions, even though individual claims recite individually defined components, none

of these claims recite all defined components and what specifically is to be "treated", in order for the skilled artisan to known how to make and use the invention, as broadly claimed, without requiring undue experimentation to determine such, as previously made of record. In other words, each claim must recite what specific receptor is to be affected for what specific disorder, in which something assayable is "treated", in order for the skilled artisan to known how to make and use the instant invention, because no universal "treatment" exists for all disorders and because no "treatment" is known or disclosed that involves "a multiplicity of different integral membrane proteins", by definition. Each unique disorder involving dysfunctional receptors is characterized by its own unique and specific dysfunctional receptor, which is either not known, disclosed or claimed.

Applicants then argue that "[f]or each disorder, the integral membrane protein must, by definition, be known in order for administration of an antagonist to be indicated". The Examiner agrees. However, in contrast to Applicants' subsequent analysis on pages 3-4 of the response, for example, adrenergic receptors are not related to the cholinergic dysfunction that characterizes Alzheimer's disease, the NMDA-glutamate receptors overstimulation that characterizes stroke/ischemia, or the dopaminergic dysfunction that characterizes Parkinson's disease, etc. Only specific receptors can have a "multiplicity of different antagonist peptides", by definition. It is suggested that combining, for example, the limitations of claims 25-27, 30-31, 33-34, all without (h) or "conservative amino acid substitution variant[s]", with claims 18 & 28, 18 & 32 and 18 & 35, respectively, may obviate this rejection. Otherwise, the claims are clearly not

commensurate in scope with that disclosed within the specification (e.g., as it relates to involving solely the adrenergic receptor for all broadly claimed disorders, or the EGF receptors argued on pages 5-6 of the response, etc.), or that well known recognized within the art involving unique dysfunctional receptors for unique disorders, for the reasons made of record.

As previously made of record,

1) peptides "associated with specific receptor overactivity" have not been claimed; nor have they been adequately described.

2) although adrenergic receptor antagonists may be accepted as therapeutic agents for treatment of hypertension (i.e., as described on page 23, lines 29-30), the specification provides apparently contradictory guidance on how "heart rate [can be decreased] using a β1-adrenergic-specific peptide" (pg. 41), because vehicle alone gave a comparable change in blood pressure when compared to administrating the β1-adrenergic-specific peptide (pg. 42). Thus, treatment of hypertension still does not appear to work using these transmembrane peptide molecules (i.e., as it relates to claims 30-31); thereby, still not being commensurate in scope for knowing how to effect an measurable phenotype as it relates to the *generic* adrenergic receptors currently claimed, as previously made of record.

3) although theophylines may work on adenosine receptors as anti-asthmatics, and caffeine may have antidepressant effects though antagonizing adenosine receptors, the claims still do not recite using any specific peptide to specifically "decrease asthma" or "decrease depression" or "decrease arrhythmia" through "antagonizing specific adenosine receptors" (i.e., A1, A2a, A2b or

A3), which are further unknown, or not adequately conceptualized within the instant specification, as it relates to any specific disease state, as previously made of record. Further, in contrast to Applicants' assertions on page 4 of the response, only structurally defined molecules can be "antagonists" for structurally defined receptors, by definition. Defining antagonists by "particular functional characteristics" does not address the issues concerning this aspect of the rejection. Analogously, it was held in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) that:

> Appellants have not chosen to claim the DNA [product] by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA [product] segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

Thus, in contrast to Applicants' assertions, merely reciting biologically functionally equivalent components that are otherwise required to successfully practice the instant invention, does not enabled that broadly claimed under 35 USC 112, first paragraph, as previously made of record. Moreover, there is no nexus for any expectation that merely administrating transmembrane-specific peptides for affecting one symptom of one disorder can be extrapolated to "treating" the full scope of symptoms encompassed by the current claim language, for the reasons made of record.

4) EGF receptors remain not representative of all "neoplastic growth in cancer" because all neoplasms are not caused by dysfunction of the EGF receptor, or due necessarily to dysfunction of any different receptor; each with their own unique structure and mode of action, as previously made of record. Again, in that the claims recite no specific "neoplastic growth for which an EGF receptor antagonist is indicated", the skilled artisan still cannot reasonably practice the invention as broadly claimed, without requiring undue experimentation to define what antagonists are specific for what G-protein receptors, which may or may not be affected in any given disease state, for the reasons made of record. Thus, in contrast to Applicants' arguments, the issue is not some dictionary definition of the word, "indication', as alluded on pages 4-5 of the response, but that Applicants do not structurally define what required components are necessary to "treat" those disorders that are affected by a specific receptor, if known, as previously made of record.

5) Again as previously made of record, GABA receptors are not representative of any different population of neurons within the brain. Nor would these intrinsically inhibitory neurons be affected by antagonists to inhibit "overactivity", based solely on drugs such as benzodiazepines, because benzodiazepines bind to "agonist sites" (see pg. 27 of the specification), versus "antagonist sites", and increase chloride influx into GABA-nergic cells, thereby inhibiting action potentials. Thus, the specification still provides contradictory evidence on how to determine how and when to successfully practice the invention, without requiring undue experimentation to discover how to make and use Applicants' invention, because no universal

mechanism exists in the art by which the skilled artisan can practice the instant invention, as claimed, for the reasons made of record. Random administration of random peptides "consist[ing] essentially of at least four conservative amino acid residues from the transmembrane domain of the relevant transporter (or a conservative substitution variant thereof)...", does not reasonably enabled the invention, as currently claimed, for these reasons made of record.

6) As previously made of record, the claims still fail to recite using any specific peptide to specifically "inhibit dopamine and/or monoamine transporters" that effect any measurable cell type, disease state, or measurable phenotype; and as such still merely constitute an invitation to discover how to make and use Applicants' invention, for the reasons made of record.

In summary, the claims remain not commensurate in scope with the limited guidance provided by the specification on how to successfully practice the instant invention without undue experimentation to discover how to make and use Applicants' invention; especially in this very unpredictable art of treating disease states that have their own unique, and unknown, etiologies, for the reasons extensively made of record.

5. Claims 18, 20-37 & 60-65 are again rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It remains unclear when "administration of an antagonist ... is *indicated*" when no such step is recited in the claims, and in which it is unknown what "disorder" is to be "treated" when none is recited, or "indicated", in the claims. Similar to

that discussed above, the dictionary definition of the word, "is indicated", does not address the rejection made of record. Nor can one reasonably determine the metes and bounds of what is being "indicated" without stating such. Thus, the claims remain incomplete and ambiguous for the reasons made of record.

The claims 18 and 36 (as well as all dependent claims) are again indefinite because of the new recitation " consisting essentially of... amino acid residues", in which a peptide is defined by its amino acid sequence and in which *different sequences still change the peptide being claimed*, by definition. Thus, although Applicants arguments are persuasive on their interpretation of "consisting essentially of", Applicants' "at least four consecutive amino acid residues" cannot "consist essentially of", by definition, and still be a "conservative amino acid substitution variant of said peptide", as further claimed.

6. In that Applicants successfully argue on page 7 of the response what "consisting essentially of" means, "which *includes additional residues* at the N- and/or C-terminus which do not alter the essential function of the peptide in the context of the invention" [emphasis added] (i.e., open claim language for any non-essential amino acid residues), this interpretation is contradictory to Applicants' position in their responses of 3/27/98 (paper #12) and 1/25/99 (paper #16), in which arguments were presented that the prior art references did not teach "peptides limited to the amino acid sequence of the transmembrane domain of the protein" (e.g., see page 7 of the 3/27/98 response and page 11 of the 1/25/99 response; as it relates to "antagonist

peptides"); therefore, closed language. Thus, because of the now open language interpretation for "consisting essentially of" by Applicants, the following rejections are re-instated, as was warned in *pp* 3 & 4 the previous Office action. It is suggested that Applicants use either "comprising" (i.e., open) or "consisting" (i.e., closed language) to avoid further confusion of what their position entails.

Claims 18, 20-22, 36 & 60-61 are again rejected under 35 U.S.C. 102(b) as being anticipated by Lofts et al., for the reasons made of record in paper #13, and as follows.

Lofts et al. teach treatment of nude mice with an effective amount of encoded WT peptide sequences (see pg. 2814, Fig. 1), which "consists essentially of " at least one transmembrane domain of the mammalian *neu*/EGF integral plasma membrane protein, such that growth of solid tumors in these mice was reduced (pgs. 2816-2817), as previously made of record.

In that "portions of the extracellular and intracellular sequences of this kinase", as previously successfully argued by Applicants, are inherently not essentially to practice the invention, the current recited claim language of "consisting essentially of" structurally meets all limitations of the claims, for the reasons previously made of record.

7. Claims 18, 20-24, 29, 36-37 & 60-61 are again rejected under 35 U.S.C. 102(e) as being anticipated by Murphy et al., for the reasons previously made of record in paper #13, and as follows.

Murphy et al. teach use of dopaminergic (col. 13, lines 29-49) and adrenergic (col. 16 line 60-col. 27, line 10) G-protein-coupled transmembrane receptor peptides in pharmaceutical compositions to "treat or prevent" G-protein-related diseases (cols. 35-37).

In that "portions of the extracellular and intracellular sequences of this kinase", as previously successfully argued by Applicants, are inherently not essentially to practice the invention, the current recited limitations of "consisting essentially of" structurally meets all limitations of the claims, for the reasons previously made of record.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and on alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
December 10, 1999

Patricia A Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER